REMARKS

Claims 1, 2, 5, 7, 10, 11, and 14 are pending. Claims 3, 4, 6, 8, 9, 12, and 13 have been canceled without prejudice.

The specification has been amended to correct the typographical error wherein the incorrect name for CPP, "3,4-bis(p-carboxyphenoxy) propane," is replaced with the correct name "1,3-bis(p-carboxyphenoxy) propane." By these amendments no new matter has been added.

Claim 1 has been amended to recite that the controlled release system comprises "4-10 wt%" of temozolomide and biodegradable "polyanhydrides." Claim 1 has been further amended to recite that "the controlled release system releases temozolomide for a period ranging from 6 hours to 4 weeks *in vivo*." Support for these amendments can be found in the specification at page 4, lines 26-29, page 8, Example 6, page 12, Table 1, and in original Claims 3 and 4. As such, no new matter has been added.

Claim 5 has been amended to change the dependency from Claim 4 to Claim 1. Claim 5 has been further amended to replace the phrase "said poly(anhydride) is one" with "polyanhydrides are." This amendment makes Claim 5 consistent with the amendments to Claim 1 and improves the readability of Claim 5. Claim 5 has been further amended to correct the typographical error wherein the incorrect name for CPP, "3,4-bis(p-carboxyphenoxy) propane," is replaced with the correct name "1,3-bis(p-carboxyphenoxy) propane."

Claim 7 has been amended to replace the term "polymeric materials" with the term "polyanhydrides." Claim 7 has been further amended to recite "the controlled release system releases temozolomide for a period ranging from 6 hours to 4 weeks *in vivo*." Support for these amendments can be found in the specification at page 4, lines 26-29, page 8, Example 6, page 12, Table 1, and in original Claims 3 and 4. As such, no new matter has been added.

Claim 10 has been amended to delete the term "said." This amendment is made to improve the readability of Claim 10.

Claim 11 has been amended to replace the term "polymeric materials" with the term "polyanhydrides." Claim 7 has been further amended to recite "the controlled release system releases temozolomide for a period ranging from 6 hours to 4 weeks *in vivo*." Support for these amendments can be found in the specification at page 4, lines 26-29, page 8, Example 6, page 12, Table 1, and in original Claims 3 and 4. As such, no new matter has been added.

Claim 14 has been amended to delete the term "said." This amendment is made to improve the readability of Claim 14.

Applicants believe the Claims are now in condition for allowance.

REJECTIONS UNDER 35 U.S.C. § 102(b)

The Office Action has rejected Claims 1 and 2 under 35 U.S.C. § 102(b), as allegedly lacking novelty over Ragab (WO 00/57867, "the '867 patent"). Specifically, the Examiner asserted that the '867 patent teaches a sustained release temozolomide formulation comprising at least 3.3% temozolomide. Applicants believe the amendments to Claim 1 overcome this rejection.

The Office Action states that "[t]he '867 patent teaches a sustained release temozolomide formulation comprising at least 3.3%" (page 4). Claim 1 has been amended to recite a range of "4-10 wt%." As such, Claim 1 is not anticipated by the '867 patent. Claim 2 further limits Claim 1 in that the controlled release system is an "implantable tablet." Because Claim 1 is not anticipated by the '867 patent, Claim 2, which depends from Claim 1, is also not anticipated.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1 and 2 under 35 U.S.C. § 102(b).

REJECTIONS UNDER 35 U.S.C. § 103(a)

The Office Action has rejected Claims 1-9 under 35 U.S.C. § 103(a), as allegedly being obvious over of the combination of the '867 patent in view of U.S. Patent 6,086,908 ("the '908 patent"). Applicants respectfully traverse this rejection.

The Office Action's states:

> [T]the '867 patent discloses a controlled release formulation comprising temozolomide and controlled release polymers. The reference is silent to the specific polyanhydride of the instant claims, however these polymers are well known in the controlled release arts. This can be seen in the '908 patent.

Not only is the '867 patent silent on the specific polyanhydride, it is also silent on controlled release formulations. The '867 patent recites at page 3, lines 21-26:

> The daily dose during the dosing period of the present invention is 40 to 150 mg/m^2/day, more preferably 40 to 125 mg/m^2/day, most preferably 75 to 125 mg/m^2/day. The daily dose may be administered as a single dose, or a multiple doses adding up to the single dose. For example a daily dose of 100 mg/m^2 may be administered as two doses of 50 mg/m^2, or four doses of 25 mg/m^2. The selected dosage may be decreased, if intolerable side effects of hematological toxicity are encountered.

A fair reading of the '867 would not cause the artisan to construe that the teachings of the '867 patent relate in any way to a controlled release formulation. When read in its entirety, the '867 patent clearly conveys that temozolomide must be administered at least daily, perhaps several times a day; suggesting controlled release is not an option. Again, the '867 patent teaches that temozolomide should be administered "most preferably for 1 or 3 weeks" followed by a rest period. The disclosure of the '867 patent juxtaposes a treatment time period that is immediately followed by a rest period. This rest period disclosure, taken together with the "daily dosage" teachings of the '867 patent, suggests that the timing of the rest period is predicated on observing the patient when each daily dose is given and that these observations determine when and how long a rest period is warranted. As such, the '867 patent suggests that an implantable tablet is not an option. Instead, the '867 patent suggests that it is important to administer temozolomide under careful patient monitoring such that the dosage can be adjusted (by frequency of administration) and the rest period can begin when patient conditions demand such. Therefore, the only disclosure in the '867 patent that is germane to the present rejection, is the disclosure that temozolomide is used to treat cancer; and that information can be found in a Physician's Desk Reference.

As it relates to the '908 patent, the Office Action states

> The reference [is] silent to spray-drying the dissolved polymer formulation in order to arrive at the microparticles, however the process of the '908 patent results in the same controlled release implantable tablet as the instant claims.
>
> With these things in mind it would have been obvious to combine the cancer agents of the '867 patent into the formulation of the'908 patent in order to provide a stable long term implantable device.

The '908 patent discloses implants that have a plurality of layers that can provide a differential release rate; not a controlled release "to 4 weeks" as recited in Claim 1. Administration of temozolomide is only accomplished within strictly controlled parameters as taught in the '867 patent. The '908 patent teaches the delivery of water-soluble dyes (model compounds) into 10 mL of 0.1 M phosphate buffer at pH 7.4. This is not an *in vivo* test as disclosed by Applicants, but instead a test to see if the polymers *per se* will release their ingredients under the osmolality conditions of a standardized buffer. The result of this disclosure would be construed by the artisan as teaching the release of a small amount of a highly colored dye into an aqueous solution under optimal conditions of mass action. This does not demonstrate, nor would it be suggestive that, temozolomide can be controllably released into tissue.

By contrast, Applicants disclose *in vivo* results that are summarized in Table 1 and Figures 1 and 2. As disclosed, a blank disc and three discs comprising 3%, 5%, and 10% of temozolomide are implanted into seventy animals. The results indicate, as shown in Figure 1, that Applicants' tablets can release temozolomide in varying amounts with the same approximate release rate over a period of 250 hours (10 days). What is necessary to release a pharmaceutical ingredient *in vivo* is different than the conditions necessary to release water soluble dyes into a buffered solution.

The '867 patent teaches the criticality of precise administration of temozolomide without suggesting a way to administer temozolomide other than daily by oral administration. The '908 patent teaches that a patch can be fabricated that releases a plurality of water soluble dyes. The assertion by the '908 patent that the method can be used to deliver pharmaceuticals does not obviate the requirement that in order to support this supposition, at least one example of a patch comprising a pharmaceutical should have been disclosed. The artisan would not construe that the '908 patent teaches or suggests that temozolomide can be delivered under any conditions other than those set forth in the '867 patent, *i.e.*, that temozolomide should be administered orally under closely monitored conditions.

The Office Action has rejected claims 7 and 10-14 under 35 U.S.C. § 103(a), as allegedly being obvious over of the combination of the '867 patent in view of U.S. Patent 6,086,908 ("the '908 patent") in further view of U.S. Patent 6,753,014 ("the 014 patent"). Applicants respectfully traverse this rejection.

The Office Action states:

> The '014 patent discloses a method of making stable sustainded release tablet[s] comprising forming particles of dispered drug compounds and polymers and compressing the particles into stable tablets (abstract). First solutions of polymeric materials are formed by dissolving the mixing [sic] in a solvent such as methyl [methylene?] chloride (claim 14); next active agents are combined with the solution before it is emulsified through an ultrasonic nozzle (col.5 lin. 19-35). The emulsion can be mixed with other polymers before the solvent is removed and microspheres are formed (col. 5, lin. 50-col. 6, lin. 30). The microspheres compressed into a table (col. 7, lin. 25-30). It would have been obvious to use the method of the '014 patent since many of the polymeric materials are similar to [those] of the'908 patent.

The '014 patent does not teach or suggest Applicants' methods. In fact, like the '908 patent, there is only an assertion that the method disclosed in the '014 patent can be used to deliver any pharmaceutical. There is one working example that teaches the formation of the '014 particle, however, this example does not comprise a pharmaceutical active. The second part of the working examples (Example 2) discloses a way to coat the particles formed in Example 1 such that the particles exhibit certain physical characteristics, for example, dry content, bulk density, pore size and mechanical strength. The '014 patent is silent on release rates which is critical to Applicants' disclosure.

The '014 patent relates to particles having reduced friability, *i.e.*, the ability to reduce a solid substance into smaller pieces with little effort, for exmaple, a substance that can be reduced to fibres or finer particles by the action of comparatively little pressure or friction on its mass. This can be achieved by "spray-freezing a suspension, solution or emulsion of a pharmaceutically active substance." (See col. 4, lines 19-20.) As such, the '014 patent requires freezing of an emulsion to obtain a particle having greater hardness. How this increase in hardness relates to the release rate of a pharmaceutical, especially temozolomide, is never disclosed in the '014 patent. Therefore, the artisan would not look to the '014 patent for any reason other than to decrease the friability of a coated particle.

The '867 patent is silent as it relates to the process recited in Claim 7. Moreover, as stated above, the '014 patent is silent on the release rate of **any ingredient** *per se* from the disclosed reduced friability particles. Since there is only example in the '014 patent that

discloses particles formed by the disclosed process, and those particles do not comprise an ingredient targeted for release the artisan is left to proceed with undue experimentation in order to determine if the '014 patent process is able to produce a particle having any degree of controlled release. The '908 patent relates to controlled release from a patch, not a microparticle, whereas the '014 patent discloses a microparticle having low friability. As such, the question of how decreased friability correlates to controlled release from a patch is left unanswered by the combination of the '014 and '908 patents.

Applicants respectfully request reconsideration and withdrawal of the rejection of the Claims under 35 U.S.C. § 103(a).

CONCLUSION

Claims 1, 2, 5, 7, 10, 11, and 14 are now in condition for allowance. The Office is encouraged to contact Applicants' Agent to expedite prosecution and to discuss any relevant matters.

No fee is believed to be due. However, the Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayments, to Deposit Account No. 14-0629.

Respectfully submitted,

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